REMARKS

Claims 25-34, 38-63 and 67-71 are pending. Claims 25-34, 38-52 and 56-57 have been withdrawn from examination. Claims 53-55, 58-63 and 67-71 have been examined on the merits. Claim 53 has been amended. This amendment has been made to assist the Examiner to understand the claimed invention. The amendment has not been made to obviate prior art or overcome any rejection for patentability.

The amendment finds basis throughout the specification, the essence of which is to prepare arrays of Immunoglobulin binding protein (IgBP) polypeptides or arrays of components of IgBP, the latter including C_HBP. Support for these concepts is found for example at page 10, lines 8-24, which defines an IgBP as follows:

> Immunoglobulin binding protein (IgBP): An immunoglobulin binding protein (i) comprises an amino acid sequence that is at least 75% identical to at least one framework region of a native immunoglobulin molecule (e.g., IgM, IgG, IgA, IgD, IgE, IgY kappa or lambda) and (ii) is a functional binding protein. Framework regions are described below, under "Immunoglobulins." A protein P is a functional binding protein if (1) for one molecular, ionic or atomic ligand A the K_D (P, A)$<10^{-6}$ moles/liter (preferably $<10^{-7}$ moles/liter), where K_D (X,Y)=[X][Y]/[X:Y], and (2) for a different molecular, ionic or atomic species B, K_D (P, B)$>10^{-4}$ moles/liter. Such a protein P is said to specifically bind A. Immunoglobulin binding proteins (IgBPs) generally function as a binding protein by virtue of the properties of a sequence of amino acids comprising a combining site, as defined below. An IgBP may comprise a single immunoglobulin chain or fragment thereof, multiple identical immunoglobulin chains or fragments thereof, or multiple non-identical immunoglobulin chains or fragments thereof. IgBPs include, for example, single chain antigen binding proteins, Fabs and Fvs. **Also included are heavy chain binding proteins (C_HBPs), discussed in greater detail below**.

As shown by emphasis added, the IgBP is a term that may also include C_HBP. In addition, the specification at page 10 also defines an Ig component which is a polypeptide of an IgBP.

> Component of an IgBP: a polypeptide capable of forming one or more covalent bonds (preferably disulfide bonds) with one or more other polypeptides to generate a functional binding protein. A component is not itself a functional binding protein. For example, a multimeric antibody is considered an IgBP, and the polypeptide chains that are joined by covalent bonds to form an antigen binding site are considered to be IgBP components. Examples of such components include but are not limited to heavy chains and fragments thereof, light chains and fragments thereof, J chain and fragments thereof, and secretory component and fragments thereof.

The specification starting at page 11, line 5, further defines a C_HBP as follows (emphasis added);

> Immunoglobulin heavy chain binding protein (C_HBP): **an IgBP** that (i) comprises multiple combining sites derived from (i.e., at least 75% identical to at least 25 consecutive amino acids of) either immunoglobulin light chain or heavy chain variable regions, but not both; and (ii) comprises a native heavy chain constant region sequence, or a fragment or other variant thereof, provided that the amino acid sequence of such a component is at least 75% identical to a constant region tailpiece (defined below) of a mu or alpha chain of a native immunoglobulin heavy chain. A C_HBP that comprises combining sites derived from one or more heavy chain variable regions does not comprise a combining site derived from a light chain variable region. Similarly, a C_HBP that comprises combining sites derived from one or more light chain variable regions does not comprise a combining site derived from a heavy chain variable region. Multiple C_HBP components may be covalently linked to generate a functional C_HBP, or a single polypeptide may be sufficient. Representative C_HBPs include proteins assembled from four alpha chains and one J chain, from twelve mu chains or from ten mu chains and at least on J chain.

Applicant wishes to point out that the definition of a C_HBP indicates that it is a form of a IgBP. In view of all the above definitions, one skilled in the art would understand that an IgBP includes a C_HBP which may be the sole polypeptide of the IgBP if the C_HBP exhibited the requisite binding activity, or that an IgBP may include a C_HBP and another immunoglobulin chain or fragment thereof which together with the C_HBP forms a functional binding site (e.g. a combining site formed by an Ig heavy and light chain).

Applicants further point out that the specification beginning at page 30 and extending to page 41 contains an extensive description of IgBP arrays and refers generally to IgBP or IgBP component arrays. As shown and discussed above, the term IgBP or IgBP component includes the term C_HBP. Furthermore, in one instance the specification directly alludes to makes C_HBP arrays. Specification, page 35, lines 3-4 (emphasis added) ("Within certain preferred embodiments, IgBP arrays (**preferably C_HBP arrays**) may be prepared in plants, plant cells and/or seeds."). As such one skilled in the art would understand that the discussion of IgBP arrays and IgBP component arrays includes arrays of C_HBPs. Accordingly, as there is ample basis in the specification for the amendment of claim 53, such amendment raises no issue of new matter.

Reconsideration of the application is respectfully requested in view of the arguments below.

Rejection under 35 U.S.C. §112, First Paragraph (Written Description)

The rejection of claims 53-55, 58-63 and 67-71 as allegedly failing to comply with the written description requirement is respectfully traversed. According to the Examiner, the claims contain subject matter that is not sufficiently described in the specification to convey that the inventor was in possession of the claimed invention. The Examiner asserts that the specification fails to exemplify a sequence of amino acids that is at least 75% identical to a native immunoglobulin ("Ig") heavy chain, a sequence of 25 consecutive amino acids from the Ig light or heavy chain variable region or a description of any C_HBP array. As best as the Applicants can determine, the rejection seems to be based on the assertion that no complete sequence of a C_HBP is disclosed and that full sequences of all possible members of a genus is essential to have a written description of a genus C_HBP array.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 USPQ

177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* The USPTO's approach for evaluating the written description requirement as specified in *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement*, states that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

It is respectfully submitted that the present rejection is based on a flawed understanding of the written description requirement and failure to understand the state of the art and the extent of disclosure provided by the specification. The Federal Circuit in Capon v. Eshhar recently discussed the written description requirement of a genus invention for facts that are related to those herein. Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005). According to the Federal Circuit,

> [p]recedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (copy previously provided). The present rejection, however, fails to properly consider the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue.

First, the rejection fails to consider that individual C_HBP polypeptides of the claimed array, which comprise a constant region tailpiece of a mu or alpha chain, and a 25 amino acid segment of an Ig light or heavy chain variable region, (the variable region specifically binding to a ligand with a $K_D<10^{-6}$ moles/liter or forming one or more covalent bonds with one or more polypeptides in the transfected cell which together specifically binds to a ligand with a $K_D<10^{-6}$ moles/liter), are forms of immunoglobulins which are well known in the art.

The allowance for variations in the sequence of the C_HBP polypeptides (i.e., at least 75% identity) acknowledges the well known fact that sequence variation exists and has been readily demonstrated in Ig domains. One skilled in the art can readily use this knowledge in forming the claimed C_HBP arrays. Furthermore, the present application provides numerous amino acid sequences that one skilled in the art can use to make the claimed array. For example, the specification at pages 16-17 and Table 3 provides the mu and alpha tailpiece amino acid sequences from several different species of animal. The function of the tailpiece in polymerizing with J chain is described at page 16 of the specification. Thus, not only are the sequences of the various Ig components well known but the specification provides many of these sequences from which one skilled in the art can use to prepare a suitable C_HBP array in eukaryotic cells.

In addition, the specification at pages 12-16 and Tables 1 and 2 provides amino acid sequences for Ig light and heavy chain variable regions. In particular, the consensus CDR sequences shown in Table 2 are readily useable to prepare sequences which are at least 75% identical to a light or heavy chain variable region and comprise at least 25 consecutive residues. Furthermore, the structure of variable regions of immunoglobulins, like that of the mu and alpha tailpieces, is quite well known as are the methods of sequence variability selection. In this regard, the specification cites at page 15, lines 7-9 to a well known Ig sequence database "Kabat et al., Sequences of Immunological Interest, National Institutes of Health, Bethesda, Md. 1991" and at page 24, lines 11-14 to well known algorithms to determine a percentage of sequence identity.

Because extensive knowledge concerning Ig sequences is resident in the prior art (and disclosed in the specification) and there are many tools and much expertise to prepare with reasonable predictability various recombinant forms of Ig, it must be concluded that the selection of an amino acid sequence that is at least 75% identical to 25 consecutive residues of a light or heavy chain variable region is well within the capability of the ordinary skilled artisan and fully contemplated by the inventors, evidencing that they were in full possession of the clamed array.

The statement in the rejection that written description of the claimed C_HBP array requires the specification to describe "the numerous ligands that can bind to the CHBP array such that a

specificity of binding of Kd <10-6 is obtained" (Office Action, page 8) also exemplifies a failure to properly evaluate the invention when determining written description. See Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005). To determine the affinity of a ligand for a C_HBP (e.g. an antibody) cannot be said to be anything but routine as such determinations with antibodies go back to at least the 1960s. Applicants need not specify all the various ligands that one can make antibodies to since such ligands and antibodies are well known. Obtaining new such antibodies also is routine as exemplified by the prior art and the present rejection offers no evidence to the contrary. Applicants need not specify the various possible sequences or the specific ligands to demonstrate possession of the claimed genus when such information is well known. To demand otherwise evidences a failure to properly consider the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue.

It is respectfully submitted that written description in the instant case is at least as thorough as in Capon and Eshhar, 418 F.3d 1349 (Fed. Cir. 2005) where the Federal Circuit overturned a rejection for written description affirmed by the Board of Patent Appeals and Interferences (BPAI). The claims of both Capon and Eshhar involve immunoglobulins, specifically, single chain Fv immunoglobulins expressed in cells as a fusion to an endogenous protein. The specification did not disclose the full sequence of the various immunoglobulins and chimeric proteins but disclosed procedures for identifying and obtaining them and cited to other sources for the sequences.

> Eshhar's specification contains the nucleotide sequences of sixteen different receptor primers and four different scFv primers from which chimeric genes encoding scFvR may be obtained, while Capon's specification cites literature sources of such information. Eshhar's specification shows the production of chimeric genes encoding scFvR using primers, as listed in Eshhar's Table I. Capon stated that natural genes are isolated and joined using conventional methods, such as the polymerase chain reaction or cloning by primer repair. Capon, like Eshhar, discussed various known procedures for identifying, obtaining, and linking DNA segments, accompanied by experimental examples.

Id. at 1356. The BPAI concluded that the Capon and Eshhar specifications lacked sufficient written description because they did not contain the full sequences of the chimeric proteins.

> The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than the specific examples.

Id. However, the Federal Circuit held that the BPAI, "erred in ruling that §112 imposes a per se rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field." *Id.* at 1360.

The rejection relies heavily on an assertion of unpredictability in the art as of the filing date and cites to a publication by one of the inventors, Hiatt et al. "Monoclonal antibody engineering in plants" FEBS Lett. 1992 Jul 27;307(1):71-5, as well as an article by Choi et al. "A new approach for the identification and cloning of genes: the pBACwich system using Cre/lox site-specific recombination" Nucleic Acids Res. 2000 Apr 1;28(7):E19.

In response, Applicants provide herewith a declaration under Rule 1.132 by inventor, Dr. Andrew Hiatt. As discussed therein, Dr. Hiatt disputes the Examiner's contention that these references support that, as of the filing date, the relevant field was unpredictable. According to Dr. Hiatt, the Examiner's reliance on only two sentences of his 1992 publication is misplaced because the quoted statement no longer is relevant. Hiatt Declaration, ¶ 3. As he indicated, 1992 was only a few years after his initial breakthrough that antibodies could even be produced in plants, and that a lot has been accomplished in the interim. *Id.* Dr. Hiatt supports his conclusion by citation to Giddings, et al. in Nature Biotechnology, vol. 18, p. 1151-56 (2000) (copy attached to the Hiatt Declaration). Giddings is noted to refer to Hiatt's initial publication on antibody expression in 1989 and to conclude that "a considerable amount of effort has been invested in developing plants for antibody (or "plantibody") production" since Hiatt's discovery and cites to various references describing techniques for transfecting genes into a wide variety of plants. Hiatt Declaration, ¶ 3. Hiatt concludes that literature shows that the ability to use plants to express foreign genes has increased dramatically in the eight years since his 1992 reference, and

that a proper reading of his 1992 reference would have led one to seek other evidence supporting this conclusion.

Dr. Hiatt also disputed the relevance of the Choi et al. reference to the claimed invention. Hiatt Declaration, ¶ 4. According to Hiatt, Choi et al. describes methods for site-specific plant transformation of large DNA inserts used in gene expression experiments which is different from the claimed method of creating a library of antibody genes to find new antibody specificities. *Id.* While acknowledging that the Choi et al. method is appropriate for large segments of DNA (up to 350 kb), in Hiatt's opinion, the claimed methods do not need this property. *Id.*

In view of Dr. Hiatt's analysis, neither Hiatt et al., 1992 nor Choi et al., 2000 support the Examiner's premise that the art was unpredictable.

Applicants respectfully submit that when the instantly claimed invention is properly considered along with the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue, one must conclude that the written description requirement has been satisfied by the present specification. Accordingly, reconsideration and withdrawal of the rejection is respectfully urged.

Rejection under 35 U.S.C. §112, Second Paragraph

The rejection of claims 53-55, 58, 63 and 67-71 as allegedly being indefinite because of claim 53 is respectfully traversed. According to the Examiner, allegedly does not clearly indicate whether the "the individual location in the array is transfected with a library of polynucleotide [sic] or each member of the library is comprised in each location of the array." Applicants are at a loss to understand what language specifically relates to this alleged indefiniteness.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." Credle v. Bond, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). Recognizing that the English language is not always precise, the settled law has established that the essential inquiry in a definiteness

analysis is whether the claims set out and circumscribe the claimed subject matter with reasonable particularity. See, e.g., MPEP § 2173.02; see also, Miles Laboratories, Inc. v. Shandon, Inc., 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added). Definiteness is not analyzed in a vacuum, but in light of the content of the specification, and with the knowledge available to the skilled artisan.

Claim 53 makes clear that that the array comprises at least two eukaryotic cells that result from transfecting a population of eukaryotic cells with a library of at least two different C_HBP polynucleotides wherein said eukaryotic cells are each transformed with a different polynucleotide of said library of at least two different C_HBP polynucleotides. It is well understood by one skilled in the art reading Applicants specification that this claim refers to transfecting a population of cells with a library (i.e. a mixture) of polynucleotides encoding least two different C_HBP polynucleotides and that the eukaryotic cells are each transformed with a different polynucleotide of the library. One skilled in the art would not reasonably read the claim as the Examiner asserts to mean that one transfects individual cells at each location with the specified library of polynucleotides. Definiteness is not analyzed in a vacuum, but in light of the content of the specification, and with the knowledge available to the skilled artisan. Rather, all that is required is that, when the claims are read in the light of the specification, the skilled artisan is reasonably apprised of the scope of the invention. Applicants respectfully submit that the present claims meet this definiteness standard. Accordingly, reconsideration and withdrawal of the rejection is earnestly solicited.

New Matter Rejection

The rejection of the claims as containing new matter in view of the language "CHBP array in eukaryotic cells that result from transfecting with a library polynucleotides" is respectively traversed. According to the examiner, the specification describes arrays of IgBPs but not C_HBP.

The response to this rejection is found in the above description of support in the specification for the currently amended claims. As discussed therein, the specification beginning

at page 30 and extending to page 41 contains an extensive description of IgBP arrays and refers generally to IgBP or IgBP competent arrays, *which terms clearly encompass C_HBP*. See, e.g., specification, page 35, lines 3-4 (emphasis added) ("Within certain preferred embodiments, IgBP arrays (**preferably C_HBP arrays**) may be prepared in plants, plant cells and/or seeds."). As such one skilled in the art would understand that the discussion of IgBP arrays and IgBP component arrays includes arrays of C_HBPs. Accordingly, reconsideration and withdrawal of the rejection is earnestly solicited.

Rejection under 35 U.S.C. §102 (Anticipation)

The rejection of claims 53-55, 58, 63 and 67-71 as allegedly lacking novelty over Ma et al. (Eu J Immunol) is respectfully traversed.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also, MPEP §2131. The Examiner bears the initial burden of establishing a *prima facie* case of anticipation. Only when a *prima facie* case has been established does the burden shift to the applicant to rebut the *prima facie* case. See, e.g., In re Morris, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

The rejection states that Ma discloses at pages 132-133 twenty two transgenic plants regenerated following transformation with heavy and light chains containing constructs and that this constitutes and array as presently claimed.

Applicants, however, point out that the claimed C_HBP array results from transfecting a population of cells with a library of at least two different C_HBP polynucleotides. No such library is described anywhere in Ma et al. In all cases, the transformants produced by Ma et al. are obtained by transfecting with a single polynucleotide. The reference, therefore, fails to disclose each and every element of the claims. See In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also, MPEP §2131. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Respectfully submitted,

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